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ORIGINAL RESEARCH

Effect of Modafinil on Core Temperature During Sustained Wakefulness and Exercise in a Warm Environment

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MCLELLAN TM, DUCHARME MB, CANINI F, MOROZ D, BELL DG, BARANSKI JV, GIL V, BUGUET A, RADOMSKI MW. *Effect of modafinil on core temperature during sustained wakefulness and exercise in a warm environment.* **Aviat Space Environ Med 2002; 73:1079–88.**

Background: Previous studies have revealed that modafinil elevates resting core temperature during periods of sustained wakefulness. The purpose of this study was to examine the effects of modafinil on core temperature during rest and exercise throughout 40 h of sustained wakefulness in a warm environment. ***Methods:*** Ten males performed a drug session (three 100 mg doses per day) and a placebo session that involved a control day, 40 h of sustained wakefulness, and a recovery sleep. For 38 h of the sustained wakefulness, subjects were exposed to 30°C with 50% relative humidity. During the afternoon of both days of wakefulness and during the early morning of the second day, subjects performed 2 h of exercise at 60% V_{O_2max} while exposed to the warm environment. ***Results:*** The data revealed that rectal temperature (T_{re}) was elevated at rest 0.15–0.2°C following modafinil ingestion throughout the period of sustained wakefulness. This increase in body temperature at rest was due to an increase in heat production during the first day of wakefulness followed by a lower evaporative heat loss during the second day. During exercise, an inconsistent effect of the drug on T_{re} was observed throughout the 38-h period. On the first afternoon, the impact of modafinil on T_{re} was no longer evident after 20 min of exercise. In contrast, during the early morning and afternoon of the second day, the effects of the drug on T_{re} at rest remained during exercise. For seven subjects who had T_{re} data for 80 min during all exercise periods, T_{re} during the placebo session was 38.9, 38.4, and 38.7°C after 80 min of exercise for periods one, two, and three, respectively, whereas the corresponding values during the modafinil session were 38.8, 38.7, and 38.9°C. ***Conclusion:*** With a greater cumulative dose of the drug, T_{re} remained elevated throughout the exercise period to an extent similar to the increase observed under resting conditions when compared with the placebo condition.

Keywords: partitional calorimetry, heat storage, skin temperature, heart rate

MODAFINIL is a relatively new synthetic psychostimulant approved for the treatment of narcolepsy (6). Modafinil has also been used for combating the detrimental effects of sustained wakefulness on cognitive performance that can occur during sustained military operations (4,3,9,35). One of the clear benefits of the drug is that, unlike amphetamines, it permits subjects to sleep when an opportunity is presented (10). For the military this is quite important for if a nighttime mission were delayed or aborted personnel could still sleep. Modafinil has been purported to act centrally as an α_1-adrenergic agonist (17), but more recent evidence has shown that modafinil inhibits γ-aminobutyric acid (GABA) release in the cerebral cortex through the possible involvement of serotonergic (5-HT_3) receptors (19) leading to secondary increases in dopamine levels (18,20). Recently, Lin et al. (27) have proposed a hypothesis of cerebral disinhibition to account for the action of modafinil for increasing vigilance and wakefulness without the side-effects of other pharmacological agents such as amphetamines (10).

However, the use of modafinil may affect core temperature. Studies by Brun et al. (9) and Pigeau et al. (35) have revealed that the normal fall in core temperature during the early morning hours while at rest was suppressed following a 300 mg dose of modafinil in the late evening. Following a subsequent dose at 0800 in the morning, core temperature at rest was increased approximately 0.4°C for the remainder of the sleep-deprived day compared with the placebo trial (9). Neither of these studies attempted to delineate whether the increase in core temperature that follows modafinil ingestion was due to an increase in heat production and/or a decrease in heat loss. The rise in core temperature following modafinil ingestion has not been a consistent observation, however. Bourdon et al. (8) observed no change in rectal temperature (T_{re}), mean skin temperature ($\bar{T}_{sk}$), or the rate of heat production during exposure to a thermoneutral environment of 29°C at

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This manuscript was received for review in July 2001. It was revised in February and June 2002. It was accepted for publication in July 2002.

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rest for 3 h following the ingestion of a 200 mg dose of modafinil.

GABAergic mechanisms have been implicated in the control of body temperature through modulations of both sympathetic adrenergic (32) and cholinergic (21) activity, and/or through direct effects on firing rates of warm sensitive neurons in the anterior hypothalamic region of the rat brain (34). Specifically, injections into the hypothalamus of rats with the GABAergic agonist, muscimol, led to decreases in the firing rate of adrenergic nerves which innervates interscapular brown adipose tissue and reduced heart rate, metabolic rate, and core temperature (32). Conversely, intraperitoneal injections in the rat of the GABAergic antagonist, bicuculline, produced an increase in body temperature during exposure to both 28°C and 40°C (21). Modafinil, through its inhibition of GABA release, likewise may increase core temperature.

Whether the ingestion of modafinil also affects core temperature during exercise has not been studied. Recent findings from Gonzalez-Alonso (22) have shown that the core temperature tolerated at exhaustion for endurance athletes is independent of the rate of heat storage and the initial starting temperature. Thus, if the increases in core temperature noted under rest conditions with modafinil are also evident during exercise, individuals may reach a critical core temperature sooner. Exercise or work times in the heat may be reduced, therefore, in proportion to the magnitude of the increase in core temperature at rest following the ingestion of modafinil.

Sustained wakefulness also may interact with thermoregulatory processes during exercise. Sustained wakefulness for approximately 30 h is known to reduce the sensitivity of the sweating and cutaneous vasodilatory responses during exercise (25,37), increase the threshold temperature for the onset of sweating (15), and decrease the threshold temperature for the onset of cutaneous vasodilation (25). Some studies (37), but not all (15,25), have reported a greater increase in core temperature during exercise following a period of sustained wakefulness. Since modafinil has been shown to be an effective treatment in reducing the negative consequences of sustained wakefulness on cognitive performance (4,35) and since it has been used during sustained military operations (10), which may include prolonged work periods, it would be worthwhile to know if the drug shows any interactive effects with sustained wakefulness during exercise

The purpose of the present study, therefore, was to examine the impact of modafinil ingestion on core temperature during 40-h of sustained wakefulness at 30°C both at rest and during repeated exercise periods scheduled in the late afternoon when core temperature was high and in the early morning when core temperature was low. It was hypothesized that modafinil ingestion would elevate T_{re} both at rest and during exercise throughout the time of sustained wakefulness and that the exercise T_{re} response would be greater during the latter stages of sustained wakefulness regardless of drug intervention.

METHODS

Subjects

Ten non-heat-acclimatized males volunteered to participate in the study after approval was obtained from the Institute's Ethics Committee. Mean values (±SD) for age, weight, height, Dubois body surface area (A_D) (16), and $\dot{V}O_{2peak}$, were 26.8 ± 6.9 yr, 77.3 ± 8.0 kg, 1.79 ± 0.10 m, 2.00 ± 0.10 m^2, and 53.2 ± 6.1 $ml \cdot kg^{-1} \cdot min^{-1}$, respectively. Every subject was informed of all details of the experimental procedures and the associated risks and discomforts. After a medical examination to ensure that there were no medical contraindications to their participation in the experiment, each subject gave their written informed consent prior to the first day of data collection. Experiments were conducted in September for four subjects and in February for the remaining participants. Because of the influence of the menstrual cycle on temperature regulation and because sessions were scheduled 5 d apart (see below), women were not recruited for the study.

Determination of Peak Aerobic Power ($\dot{V}O_{2peak}$)

$\dot{V}O_{2peak}$ was determined on a motor-driven treadmill using open-circuit spirometry (13,28) before the series of experiments in the climatic chamber. Following 2 min of running at a self-selected pace, the treadmill grade was increased 1% · min^{-1} until subjects were running at a 10% grade. Treadmill speed was then increased 0.22 $m \cdot s^{-1}$ (0.8 $km \cdot h^{-1}$) each minute until the subject could no longer continue. $\dot{V}O_{2peak}$ was defined as the highest $\dot{V}O_2$ observed over 30 s during the incremental test. Heart rate (HR) was monitored throughout the incremental test from a telemetry unit (Polar Electro PE3000, Stamford, CT). The highest heart rate value recorded at the end of the exercise test was defined as the individual's peak value (HR_{peak}).

Familiarization Session

Approximately 1 wk prior to the experimental sessions, subjects performed a 7-h familiarization session in the environmental chamber at 30°C and 50% relative humidity following the insertion of a rectal thermistor (Pharmaseal APC 400 Series, Valencia, CA) 0.15 m past the anal sphincter. While in the chamber, subjects practiced a computerized cognitive test battery, were instrumented with recalibrated heat flux transducers incorporating a skin thermistor (Model Concept Engineering, Old Saybrook, CT), and completed a 30-min rest and 2-h exercise period to simulate the thermoregulatory and heart rate data collection protocol that would be implemented during the experimental sessions The exercise period was used to establish individual work rates that would increase T_{re} to between 39°C and 40°C by the end of the 2 h.

Experimental Design

All subjects performed a drug and placebo session in random order separated by 5 d. A schematic of the experimental design is shown in **Fig. 1**. Subjects arrived at the Institute at 0700 of the control day. After inserting

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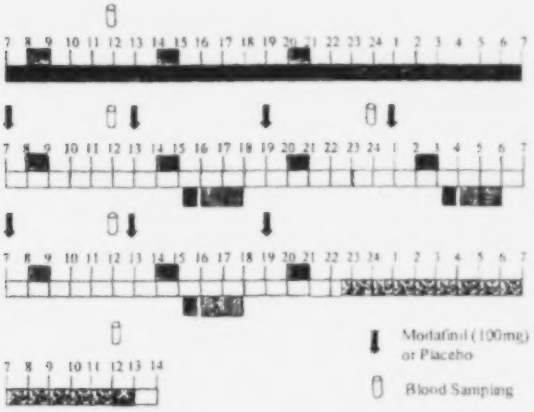

Fig. 1. A schematic representation of the experimental design that included a baseline control day followed by 38 h of sustained wakefulness at 30°C and a subsequent recovery day. A cognitive test battery was administered every 6 h while awake and modafinil or placebo was ingested every 6 h during the time of sustained wakefulness. Thermoregulatory responses were evaluated during three 30-min rest and 2-h exercise periods that represented the afternoon of both days and the early morning of the second day of sustained wakefulness. The capsule administered at 1900 h of the first day of sustained wakefulness was placebo during both sessions.

their rectal thermistor that was connected to a data logger (ACR Systems Inc., Surrey, B.C.), subjects remained in a comfortable environment of approximately 22°C and 50% relative humidity until the next morning. The findings from the cognitive test battery that was administered every 6 h during wakefulness are reported elsewhere (5). Food and electrolyte drinks and juices were provided throughout the control day but the composition of the diet was not controlled. However, an on-site cafeteria provided a mixed composition of food during both control days for the drug and placebo sessions. Caffeinated beverages were not allowed. For the remainder of the control day, subjects studied, watched videos, or played computer games until they retired at 2230 h.

Subjects were awakened at 0630 the next morning. By definition, this represented the beginning of the sustained wakefulness time. At 0700, subjects entered the environmental chamber that was controlled at 30°C and 50% relative humidity with a wind speed less than 1 m $\cdot$ s^{-1}. They remained awake in the chamber for the subsequent 38 h until 2100 h of the next day, following the completion of the last cognitive test battery. The subjects then showered and retired to bed at 2230 h for a total sustained wakefulness time of 40 h.

Placebo (metamucil) or modafinil (100 mg) gelatin capsules were administered in a double-blind manner every 6 h while in the chamber beginning at 0700 h. The capsules given at 1900 h of the first day were placebo during both sessions such that the total dose of modafinil was 300 mg in a 24-h period.

During the sessions, the composition of the food provided was not controlled and consisted of order-out meals such as pizza, chicken, and sandwiches together with fresh fruit and snacks. However, records were kept of the food that was ordered during the first session and replicated for each subject during their second visit. Although records were not kept of the total amount of food consumed at each meal, subjects did not refuse to eat the food that was provided. In addition, subjects were encouraged to drink electrolyte drinks, such as Gatorade® and Powerade®, fruit juices, and water throughout the time of sustained wakefulness in the chamber. The temperature of all ingested fluid was controlled at 37°C to minimize any drink-induced effects on core temperature. Subjects wore jogging shorts, socks, running shoes, and occasionally a T-shirt while they were exposed to the warm temperature.

Rest and Exercise Periods

From 1515 to 1800 h of the afternoon of both days and from 0315 to 0600 h during the morning of the second day of sustained wakefulness, partitional calorimetric determinations of heat storage were made during a 30-min period of seated rest and a subsequent 2-h treadmill exercise period. No T-shirts were worn during these data collection periods. During the exercise, subjects either initially walked at 5.6 km $\cdot$ h^{-1} with a 7–14% grade or ran at 8.8 km $\cdot$ h^{-1} on the level. Based on the T_{re} response from the familiarization session, treadmill speeds and grades were then individually adjusted at 30-min intervals in an attempt to increase T_{re} above 39°C by the end of the exercise period. Adjustments in treadmill speed and grade throughout the first exercise period were replicated for all subsequent exercise periods. Each exercise period continued for a maximum of 120 min or until either T_{re} reached 40.0°C, heart rate remained at or above 95% of HR_{peak} for 3 min, nausea, dizziness, or injury precluded further exercise, or the subject asked to stop exercising.

Approximately 3 h prior to initiating the data collection for heat storage, subjects were instrumented with a heart rate monitor and 7 heat flux transducers. Nude body weight, which included the weight of the heat flux transducers, rectal thermistor and supporting harness, and heart rate monitor, was measured at the beginning and end of the rest period and at the end of the exercise period. Immediately prior to initiating data collection during the rest and exercise periods, the subject's heat flux transducers and rectal thermistor monitoring cables were connected to a computerized data acquisition system (Hewlett-Packard 3497A control unit, 236-9000 computer, and 2934A printer). Every minute, average values for T_{re} and a 7-point weighted mean skin temperature (T_{sk}) (23) were recorded and printed by the data acquisition system. HR was recorded every 10 min from the display on the telemetry receiver. Subjects were given no fluid during the rest period but 300 ml of

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37°C water was consumed immediately prior to and at 30-min intervals during the exercise period.

Differences in nude weights after the rest and exercise periods were corrected for respiratory and metabolic weight loss (see below) and fluid intake. Sweat production rates were calculated as the difference in nude weights before and after the rest and exercise periods. Following each exercise period, subjects were rehydrated with carbohydrate and electrolyte drinks. The total volume provided for each subject was calculated to offset the change in nude mass that was recorded after the exercise period.

Open-circuit spirometry was used to determine expired minute ventilation and oxygen consumption ($\dot{V}O_2$) for 2–3 min every 15 min during rest and every 20 min during exercise. Respiratory water loss was calculated using the measured $\dot{V}O_2$ and the equation presented by Mitchell et al. (31). Metabolic weight loss was calculated from $\dot{V}O_2$ and the respiratory exchange ratio using the equation described by Snellen (38).

Immediately following the gas exchange measurement, subjects were asked to provide whole body ratings for thermal discomfort (RTD) at rest and during exercise and for perceived exertion (RPE) during exercise (7).

Blood Sampling

A venipuncture technique was used to obtain blood from an antecubital vein for the determination of plasma modafinil levels at noon of the control day, each of the days of sustained wakefulness, and the following recovery day. Modafinil levels were determined using gas chromatography-mass spectrometry with electron capture negative ion chemical ionization. At the same time during the days of sustained wakefulness and at midnight of the first day in the chamber, blood was also obtained to measure serum osmolality, calculated from sodium, glucose, and urea nitrogen determinations (Stat Profile Ultra, Nova Biomedical, Waltham, MA), as an indicator of hydration status prior to each exercise period.

Calculation of Heat Storage

The rate of heat storage during the rest periods (S in $W \cdot m^{-2}$) was calculated from the heat balance equation,

$$S = M - W \pm (C + R + K) \pm C_{res} - E_{res} - E_{sk} \quad \text{Eq 1}$$

During the exercise periods, it was not possible to accurately determine evaporative heat loss, E_{sk}, from whole body sweat rates obtained from changes in nude body weights. Dressed weight was not recorded. As a result, the required evaporative cooling, E_{req}, was determined from the heat balance equation as,

$$E_{req} = M - W \pm (C + R + K) \pm C_{res} - E_{res} \quad \text{Eq 2}$$

Details about the specific equations used to calculate the rate of metabolic heat production, M, the external rate of work performed, W, when subjects walked on the treadmill with an elevation, respiratory evaporative heat loss, E_{res}, and convective heat loss, C_{res}, have been presented elsewhere (29).

The rate of radiative and convective dry heat exchange, R and C, was calculated using the sum of the linear radiative heat transfer coefficient, h_r (4.6 and 5.1 $W \cdot m^{-2} \cdot °C^{-1}$ for sitting and standing, respectively (2)), and the convective heat transfer coefficient, h_c (3.1 $W \cdot m^{-2} \cdot °C^{-1}$ for sitting (33) and values between 7.8 and 9.2 $W \cdot m^{-2} \cdot °C^{-1}$ for treadmill walking and running speeds between 5.6 and 8.8 $km \cdot h^{-1}$, respectively (33)) and the difference between $\bar{T}_{sk}$ averaged over each 10-min interval and the chamber temperature of 30°C, according to Nishi (33) as

$$R + C = (h_c + h_r)(\bar{T}_{sk} - 30) \quad \text{Eq 3}$$

Although heat flux transducers are used for the measurement of dry heat loss, we were uncertain as to the influence of evaporative heat loss on the heat flux across the transducer during periods of heavy sweating. Thus the transducer was used to measure only skin temperature and dry heat loss was estimated from the equation above. The rate of conductive heat transfer, K, was considered to be negligible.

During the experiments conducted in February ($n = 6$), evaporative heat loss from the skin, E_{sk}, was determined at rest using sweat evaporation (SE in $g \cdot m^{-2} \cdot h^{-1}$) measured with an evaporimeter (Servo Med, Kinna, Sweden) positioned on the chest and the latent heat of vaporization, λ, of 675 $W \cdot h^{-1} \cdot kg^{-1}$ as,

$$E_{sk} = SE \cdot \lambda \cdot 1000^{-1}, \quad \text{Eq 4}$$

We realize that there are regional differences in sweat output over the body (14,24) but the chest was chosen for ease of access during the seated rest period.

Statistical Analyses

Tabular data are presented as mean values and the standard deviation of the mean. The standard error of the mean is used for presentation in the figures. Rest and exercise data were analyzed separately. A two-factor (session and period) repeated measures ANOVA was used to evaluate any differences between the sessions and among the rest or exercise periods for osmolality, sweat rate, sweat evaporation, average metabolic rate, heat storage, and tolerance time. A three-factor (session, period, and time during exercise) repeated measures ANOVA was performed for evaluating the changes in RPE, TC, $\dot{V}O_2$, HR, T_{re}, and $\bar{T}_{sk}$ during the sessions and throughout the rest and exercise periods. To correct for the violation of the sphericity assumption with the repeated factors, a Huynh-Feldt correction was applied to the F-ratio. When a significant F-ratio was obtained, a Newman-Keuls post-hoc analysis was used to isolate differences among treatment means. For all statistical analyses, the 0.05 level of significance was used.

RESULTS

Indices of Hydration Status

Nude body mass prior to each rest and exercise period was not affected by modafinil but a significant 1% reduction was recorded prior to the last rest and exercise period compared with the other two periods. How-

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TABLE I. COMPONENTS OF THE HEAT BALANCE EQUATION USED TO DETERMINE THE RATE OF HEAT STORAGE DURING 30 MIN OF REST IN THE AFTERNOON OR MORNING OF 38 H OF SUSTAINED WAKEFULNESS AT 30°C AND 50% RELATIVE HUMIDITY

	Day 1 (1515–1545 h)		Day 2 (0315–0345 h)		Day 2 (1515–1545 h)	
	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil
Metabolic Rate ($W \cdot m^{-2}$)	61.2 (9.9)	69.8† (12.1)	63.6 (5.8)	59.4 (9.3)	64.0 (5.1)	67.2 (12.4)
Dry Heat Loss ($W \cdot m^{-2}$)*	34.1 (2.5)	34.7 (2.1)	31.4 (3.0)	33.0 (1.9)	32.9 (3.6)	35.3 (2.6)
Respiratory Heat Loss ($W \cdot m^{-2}$)	4.5 (0.7)	5.1† (0.9)	4.6 (0.4)	4.3 (0.7)	4.7 (0.4)	4.9 (0.9)
Sweat Evaporation Rate ($W \cdot m^{-2}$) ($n = 6$)	9.1 (1.8)	7.9 (3.1)	16.0† (9.5)	9.5 (4.8)	18.7† (9.0)	8.8 (2.6)
Rate of Heat Storage ($W \cdot m^{-2}$) ($n = 6$)	16.2 (9.0)	19.3 (10.5)	11.9 (6.9)	16.2 (5.8)	8.7 (10.4)	19.2 (13.4)

Values are means (SD) for $n = 10$ unless otherwise stated.
*Significant difference between placebo and modafinil sessions. In addition, values during both afternoon rest periods were also significantly higher than during the early morning rest period.
†Significantly different from corresponding modafinil session and placebo session of day 1.

ever, osmolality was unaffected by the sustained wakefulness (285.0 ± 4.0, 286.5 ± 3.7, and 286.0 ± 4.5 mOsm · kgH_2O^{-1} for periods 1, 2, and 3, respectively) or ingestion of drug (286.3 ± 4.2 and 285.4 ± 4.0 mOsm · kgH_2O^{-1} for the placebo and modafinil sessions, respectively).

Plasma Modafinil

Throughout the placebo session and at noon during the control day of the drug session, modafinil was not detectable in the plasma. In contrast, at noon on the first day of sustained wakefulness (5 h following the first 100 mg dose of the drug), modafinil concentrations had increased to 1700 ng · ml^{-1}. Twenty-four hours later, following a further three 100-mg doses, modafinil levels had increased significantly to over 4300 ng · ml^{-1}. Modafinil concentrations were significantly reduced by noon of the recovery day but the values of over 3100 ng · ml^{-1} were still significantly higher than those recorded early during the first day of sustained wakefulness.

Indices of Heat Strain

There was no difference between the subjects tested in September and those tested in February for the impact of modafinil on any of the dependent measures described below. Although the subjects tested in September were probably more naturally heat acclimatized than those tested in February, the treadmill speeds and grades were set on an individual basis and replicated for a given subject throughout the time of sustained wakefulness for the two sessions.

Metabolic Rate

Modafinil increased the metabolic rate at rest compared with placebo (**Table I**) during the first afternoon of sustained wakefulness. Values averaged over the rest periods approximated 65 $W \cdot m^{-2}$. There was no effect of the drug or sustained wakefulness on the metabolic rate during the exercise periods (**Table II**) where values approximated 425 $W \cdot m^{-2}$.

Rates of Sweat Evaporation and Sweat Production

Sweat evaporation at rest increased during the second day of sustained wakefulness in the placebo session but this increase was not observed with the ingestion of modafinil (Table I). Sweat rates during exercise approximated 485 $g \cdot m^{-2} \cdot h^{-1}$ and were not affected by the time of sustained wakefulness or ingestion of modafinil (Table II).

Heart Rate

There was a main effect of session with a higher HR at rest being recorded with modafinil (80.4 ± 10.2 bpm) compared with placebo (75.4 ± 8.0 bpm). The drug also elevated the HR during exercise (154.0 ± 11.9 and 147.8 ± 12.3 bpm for modafinil and placebo, respectively) (**Fig. 2**). There was also a main effect of period

TABLE II. COMPONENTS OF THE HEAT BALANCE EQUATION USED TO DETERMINE THE REQUIRED EVAPORATIVE COOLING AND THE RATE OF SWEAT PRODUCTION, AND EXERCISE TIME DURING 2 H OF EXERCISE IN THE AFTERNOON OR MORNING OF 38 H OF SUSTAINED WAKEFULNESS AT 30°C AND 50% RELATIVE HUMIDITY

	Day 1 (1600–1800 h)		Day 2 (0400–0600 h)		Day 2 (1600–1800 h)	
	Placebo	Modafinil	Placebo	Modafinil	Placebo	Modafinil
Metabolic Rate ($W \cdot m^{-2}$)	422.8 (61.3)	423.9 (66.8)	422.6 (52.5)	431.6 (56.1)	414.1 (63.1)	429.3 (66.2)
Dry Heat Loss ($W \cdot m^{-2}$)*	70.1 (10.0)	73.2 (11.1)	63.5 (4.7)	68.9 (4.6)	66.0 (8.8)	69.7 (7.1)
Respiratory Heat Loss ($W \cdot m^{-2}$)	30.8 (4.5)	30.9 (4.9)	30.8 (3.8)	31.5 (4.1)	30.2 (4.6)	31.3 (4.8)
Rate of External Work ($W \cdot m^{-2}$)	35.5 (22.0)	35.5 (22.0)	35.5 (22.0)	35.5 (22.0)	35.5 (22.0)	35.5 (22.0)
Required Evaporative Cooling ($W \cdot m^{-2}$)	286.8 (61.4)	284.8 (56.3)	293.2 (56.3)	295.9 (56.0)	282.7 (58.4)	293.0 (64.9)
Rate of Sweat Production ($g \cdot m^{-2} \cdot h^{-1}$)	500 (122)	471 (85)	478 (99)	490 (127)	477 (99)	506 (133)
Exercise Time (min) ($n = 10$)	120 (0)	120 (0)	114 (19)	120 (0)	114 (13)	111 (28)

Values are means (SD) for the 8 subjects that completed the 2 h of exercise for all trials unless otherwise stated.
*Significant difference between placebo and modafinil sessions. In addition, values during the first afternoon exercise period were significantly higher than during the early morning exercise period.

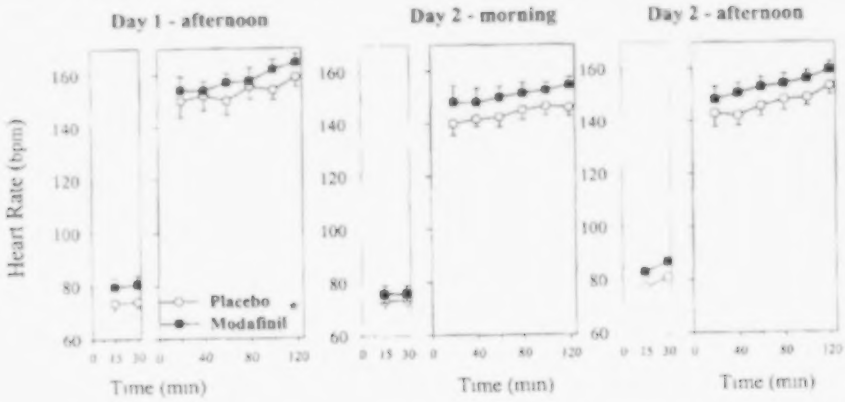

Fig. 2. Heart rate during the 2 h exercise period on the afternoon of day 1, and during the morning and afternoon of day 2 of 38 h of sustained wakefulness. Values are mean ± SEM for n = 8. The asterisk (*) indicates a significant difference between the placebo and modafinil sessions both at rest and during exercise. See the text for a more detailed description of the statistical findings.

for the HR response at rest with heart rates being significantly increased during the third rest period on the afternoon of the second day (82.1 ± 9.3 bpm) compared with 24 h earlier (77.0 ± 9.4 bpm) or the early morning of the second day (74.6 ± 8.2 bpm). During exercise, there was also a main effect of period which revealed that the HR averaged over the 2 h of exercise was significantly greater during the first afternoon of sustained wakefulness (155.7 ± 13.0 bpm) compared with the early morning (147.0 ± 11.7 bpm) or afternoon (150.1 ± 11.3 bpm) of the second day. These latter two values were not significantly different.

Rectal Temperature

Regardless of the order of drug or placebo intervention, the T_{re} response throughout the second control day which followed 5 d after the first 40-h of sustained wakefulness was not different from the response during the first control day. In addition, throughout the control day, T_{re} was not different prior to the placebo (36.85 ± 0.42°C) and modafinil (36.81 ± 0.35°C) sessions. However, there was a significant main effect of the drug on T_{re} throughout the non-exercise time of sustained wakefulness with higher values of 0.14 ± 0.25°C being recorded as early as 90 min following the first 100 mg dose of modafinil (**Fig. 3**). The T_{re} response during the 30-min rest periods and subsequent 2-h exercise periods is shown in **Fig. 4**. Problems with maintaining the insertion of the rectal probe prevented the collection of reliable data from all subjects during all of their exercise periods. Data are presented in Fig. 4, therefore, for the seven subjects whose probes remained inserted for at least 80 min of all of the exercise periods during the placebo and modafinil sessions.

During the rest periods, T_{re} was significantly increased during the modafinil session. There was also a significant main effect of period on T_{re} with the expected reduction in T_{re} being observed during the early morning hours. Interestingly, the response during period 3 that represented the second afternoon of sustained wakefulness did not return to levels recorded 24 h earlier. Values were lower by approximately 0.15°C during the second afternoon throughout the rest period.

During the first exercise period, the impact of modafinil on T_{re} was no longer evident after 20 min. However, T_{re} was significantly increased throughout the other exercise periods with the ingestion of modafinil (Fig. 4) compared with placebo. There was also a significant main effect of period for both the placebo and drug sessions with the T_{re} response during the afternoon exercise periods being higher than the results of the morning session (period 2). With placebo, the T_{re} response during period 3 that represented the second afternoon of sustained wakefulness was significantly lower than the response observed 24 h earlier during period 1, whereas this was not the case following modafinil ingestion.

Mean Skin Temperature

Modafinil also elevated $\bar{T}_{sk}$ both at rest and during exercise throughout the time of sustained wakefulness

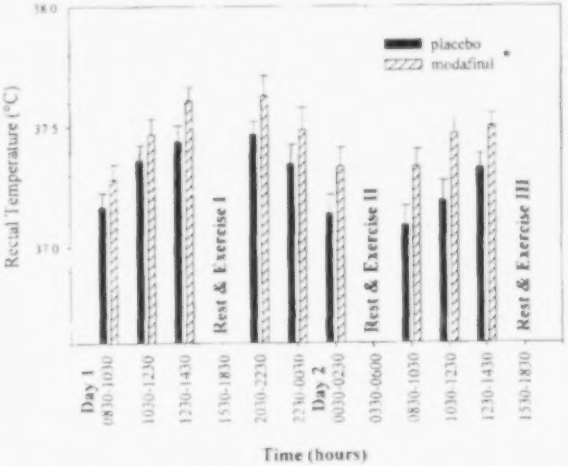

Fig. 3. Resting rectal temperature averaged over 2 h intervals throughout 38 h of sustained wakefulness during the placebo and modafinil sessions. Values are mean ± SEM for n = 10. The asterisk (*) indicates a significant difference between the placebo and modafinil sessions. There was a main effect of time and a main effect of session on the resting temperatures.

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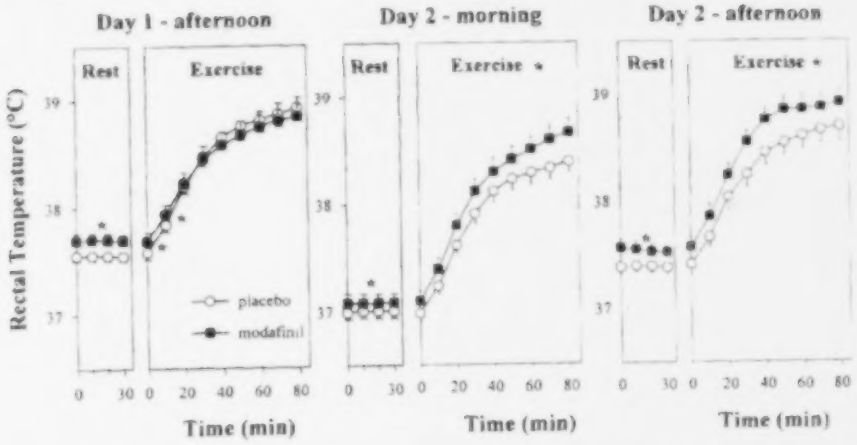

Fig. 4. Rectal temperature during 30 min of rest and a subsequent 80 min of exercise during the afternoon of day 1, and during the morning and afternoon of day 2 of 38 h of sustained wakefulness. Values are mean ± SEM for n = 10 during rest and n = 7 during exercise. The asterisk (*) indicates a significant difference between modafinil and placebo. At rest, rectal temperature was significantly increased with the ingestion of modafinil. During the second and third exercise periods, modafinil significantly increased rectal temperature whereas this was not the case after 20 min of exercise during the first exercise period. See the text for a more detailed description of the statistical findings.

(Fig. 5). At rest, $\bar{T}_{sk}$ was similar during the afternoon of both days of sustained wakefulness but the values were higher than those recorded during the early morning. With exercise a main effect of period was also observed for $\bar{T}_{sk}$, where values were significantly higher during exercise period 1 compared with period 2. However, during period 3 the $\bar{T}_{sk}$ response was intermediate to and not significantly different from the results of the other two exercise periods.

Heat Storage

Partitional calorimetry revealed that S at rest was not increased ($p < 0.07$) with modafinil (18.2 ± 9.9 W · m^{-2}) compared with placebo (12.2 ± 8.9 W · m^{-2}) (Table I). However, following modafinil ingestion there was a significantly greater rate of heat production during the first afternoon of sustained wakefulness and no increase in evaporative heat loss during the second day of sustained wakefulness compared with placebo (Table I). There was no effect of session or period on E_{req} during exercise with values approximating 290 W · m^{-2} (Table II).

Thermal Discomfort and Rating of Perceived Exertion

There was no effect of session on the RTD both at rest and during exercise and there was no effect of session on RPE during exercise. RTD values at rest were 7.1 ± 0.5 and 7.2 ± 0.7 for the placebo and modafinil sessions, respectively. There was a main effect of period during exercise for both RTD and RPE with significantly higher values recorded during periods 2 and 3 on the second day of sustained wakefulness. Values for RTD averaged 8.4 ± 0.7, 8.7 ± 0.9, and 8.8 ± 1.1 over the three exercise periods, whereas, average values for RPE were 12.8 ± 1.6, 13.9 ± 1.8, and 14.1 ± 2.0.

Exercise Time

Neither modafinil nor sustained wakefulness influenced exercise time (Table II). Of the 10 subjects, 8 completed all of the 2-h exercise periods. One subject failed to complete one placebo and two drug exercise periods because of a recurrent leg injury and another subject failed to complete the last placebo exercise period complaining of exhaustion.

DISCUSSION

The findings from the present study have revealed that the ingestion of 100 mg of modafinil three times over a 24-h period is associated with elevations in core temperature of approximately 0.2°C. This increase is observed early after the initial dose (see Fig. 1) and is

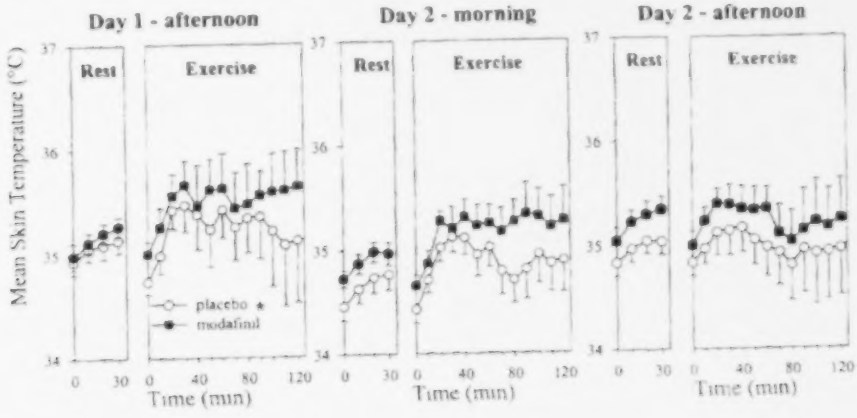

Fig. 5. Mean skin temperature during a 30-min rest and subsequent 2-h exercise period during the afternoon of day 1, and during the morning and afternoon of day 2 of a 38-h period of sustained wakefulness. Values are mean ± SEM for n = 10 during rest and n = 8 during exercise. The asterisk (*) indicates a significant difference between the placebo and modafinil sessions. Mean skin temperature was significantly elevated following modafinil ingestion both at rest and during the exercise. See the text for a more detailed description of the statistical findings.

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present at rest throughout the subsequent 38 h of sustained wakefulness in a warm environment. The rise in core temperature is consistent with the changes noted by Pigeau et al. (35) and Brun et al. (9) following 300 mg of modafinil during exposure to conditioned room environments approximating 22°C, but contrasts with the lack of effect observed by Bourdon et al. (8) following a 200 mg dose at 29°C. Since the increase in T_{re} in the present study was observed within 2 h following the initial 100 mg of modafinil, the lack of effect reported by Bourdon et al. (8) cannot be attributed to the requirement of a threshold dose or blood concentration necessary to elicit the response. Rather it is more likely that the 3 h total duration used to study the response following the 200 mg dose of modafinil (8) was insufficient and led to a Type II error. It is noteworthy that these authors reported a nonsignificant 0.3°C increase in T_{re} during the last 2 h of their observation period.

The present data have also shown that modafinil produces an inconsistent effect on the T_{re} response during exercise when the drug is combined with 38 h of sustained wakefulness. During the first afternoon of sustained wakefulness, which followed two 100 mg doses of the drug, the T_{re} response was similar to the placebo session by the end of the exercise period despite higher values being observed at rest. However, as the time of sustained wakefulness progressed and additional doses of modafinil were consumed, the T_{re} response during exercise remained elevated and consistent with the observations at rest. To our knowledge, no one has studied the effects of modafinil on core temperature during exercise, let alone studied how the drug interacts with sustained wakefulness to impact the exercise response. Thus, the present findings represent new information about the effects of the drug on human temperature regulation during exercise.

How then might we explain the consistent elevations in T_{re} at rest observed throughout the time of sustained wakefulness and the inconsistent effect recorded during the exercise periods? During the early stages of sustained wakefulness at rest, there was an increase in the rate of heat production with modafinil (see Table I). Both resting and exercise heart rates were elevated, perhaps indicative of the adrenergic action of the drug proposed earlier by Duteil et al. (17). This response is consistent with the proposed GABAergic mechanisms involved in the control of sympathetic activity in the rat (32). Thus, inhibition of GABA release following modafinil ingestion (18–20) will increase sympathetic activity and lead to an increase in resting heart rate, metabolic rate, and body temperature. However, the increase in heat production that occurred with exercise was sufficient to mask the effects of the drug early during the time of sustained wakefulness. Collectively, therefore, the early effects of modafinil on core temperature appear to be mediated through the actions of an elevated sympathetic tone on heat production at rest that are not evident when substantial increases in heat production occur during exercise. As a result, core temperature is increased under resting conditions, but the response during exercise remains matched to the relative intensity (36).

Clearly, blood (and presumably brain) concentrations and the duration of exposure to circulating modafinil levels were increasing throughout the time of sustained wakefulness as subsequent 100 mg doses of the drug were ingested. Equally apparent was the fact that T_{re} remained elevated throughout exercise periods 2 and 3 compared with the placebo session, which is consistent with the elevations recorded at rest. Exactly how the GABAergic inhibition with modafinil affects the firing rates and thermosensitivity of hypothalamic neurons that influence thermoregulatory control and effector responses is only speculative. However, the present findings strongly suggest that either a threshold circulating concentration and/or duration of exposure to the drug is required before the core temperature remains elevated during both rest and exercise. This suggestion is consistent with the observations in animal studies that while the modafinil-induced inhibition of GABA is dose-dependent in the medial preoptic area of the brain, it is threshold-dependent and stronger in the posterior hypothamlamus (19). Further, other findings have revealed that modafinil targets the lateral and anterior regions of the hypothalamus in mice and rats, respectively, (12,26) and it is possible that these targeted regions may also affect the neurons in the preoptic area of the hypothalamus that are involved in thermoregulatory control. More definitive studies are needed to clarify whether modafinil exerts a direct effect on the thermoregulatory setpoint.

The present data would suggest that there would not be an increased risk of exertional heat illness for at least 6–12 h following the initial two 100 mg doses of modafinil. Whether the same conclusion would be reached if the initial dose were increased and/or administered at a different time of day is not known. Certainly the magnitude of the effect of the drug on resting T_{re} appears greater following a 300 mg dose administered late in the evening where differences between drug and placebo sessions approximated 0.5°C (9). It is conceivable, therefore, that this dosing regimen might be sufficient to also increase the exercise T_{re} values at some time earlier than 12 h post drug ingestion. This possibility warrants further investigation given that the higher 300 mg dose of the drug has typically been administered late in the evening to counter the impairments of sustained wakefulness on cognitive performance (9,35). It is also noteworthy that our dosing regimen for the drug did not suppress the fall in T_{re} during the early morning hours as was observed in these previous studies that administered a larger single dose of modafinil late in the evening (9,35). Thus the ingestion of modafinil may not always mask the circadian influence on core temperature.

The higher T_{re} response during the latter exercise sessions following modafinil ingestion may be consistent with an earlier onset of exertional fatigue and associated symptoms of heat illness if the core temperature tolerated at exhaustion is unaffected by the starting value. This premise would be supported by the recent findings of Gonzalez-Alonso (22) which revealed for endurance athletes that the core temperature at exhaustion was not affected by variations in the starting

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core temperature or the rate of heat storage. In contrast, however, we reported that during the uncompensable heat stress environment of exercising at 40°C and wearing protective clothing, the core temperature tolerated at exhaustion was increased during trials conducted in the afternoon which offset the circadian effect on resting core temperature (29). As a result, exercise time and heat storage while exercising in the heat were unaffected by the higher afternoon resting T_{re} (29). In the present study, subjects did not exercise to exhaustion and despite core temperatures in excess of 39°C no one became ataxic or complained of nausea during the sessions throughout the three exercise periods. Thus, we were unable to study the symptomology of exertional heat illness following modafinil ingestion. It is interesting, however, that despite the higher T_{re} values during exercise with modafinil, the ratings of RTD and RPE were similar to the placebo session.

The question arises as to whether the increase in core temperature following modafinil ingestion would have a meaningful effect on exercise time in the heat. Previously we have shown that a change in core temperature at the beginning of the heat-stress exposure from 0.2–0.5°C with heat acclimation (1), hypohydration (13), or prior resting heat exposure (30) altered exercise time while wearing protective clothing from 10% following the smallest changes in core temperature to over 35% with the largest changes. Thus under conditions where personnel may be advised to take modafinil and then exercise to exhaustion in the heat one should expect a decrement in performance. The magnitude of this decrement should be proportional to the increase in core temperature that follows the dosing regimen of the drug during exercise. This might be as small as 10% with the changes observed in the present study to over 35% with the changes in core temperature noted by Brun et al. (9) following a larger 300 mg dose of the drug.

During the second afternoon of sustained wakefulness in the placebo session, T_{re}, $\bar{T}_{sk}$, and HR responses during exercise did not return to the values recorded 24 h earlier. Buxton et al. (11) have reported circadian phase delays of 60–90 min for thyrotropin and melatonin on the day following 40 min of exercise at 75% $\dot{V}O_{2max}$ scheduled at 0100 h. It is likely that we also induced a circadian phase delay by exercising at 0400 for 2 h at 60% $\dot{V}O_{2max}$. This apparent phase delay was also evident for resting T_{re}. For example, in Fig. 3, the resting T_{re} value from the placebo session averaged over the 2-h interval between 1030 and 1230 of day 2 was similar to the average recorded 26 h earlier, but less than the value observed between 1030 and 1230 of day 1. Thus our findings do not support the hypothesis that the exercise core temperature response would be greater toward the latter stages of sustained wakefulness as was reported by Sawka et al. (37). Indeed, during sessions of sustained wakefulness our data suggest that following exercise conducted in the early morning, the rise in core temperature during similar exercise in the afternoon will be less than the response observed 24 h earlier. It would not be uncommon for military personnel to be involved with repeated exercise during periods of sustained wakefulness. Thus, additional research is warranted that examines more closely the interaction between sustained wakefulness and temperature regulation during repeated exercise periods.

In summary, 100 mg doses of modafinil taken three times daily increased the resting core temperature by approximately 0.2°C throughout 38 h of sustained wakefulness in a warm environment of 30°C. The increase in core temperature at rest appeared to be mediated initially by an effect on metabolic rate. The changes in core temperature at rest following the ingestion of the drug did not remain during moderate intensity exercise performed during the first afternoon of sustained wakefulness. However, consistent changes to those recorded at rest were evident in the exercise T_{re} response during the second day of sustained wakefulness.

ACKNOWLEDGMENTS

The authors are indebted to the subjects for their commitment to finish the study and endure the discomforts of this sustained wakefulness protocol. We also thank D. Brajkovic, D. Kerrigan-Brown, C. Cian, R. Limmer, J. Pope, A. Roux, G. Seabrook, I. Smith, T. Unruh, and J. Zamecnik for their technical assistance.

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